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Letters to the Editor

Dear Editor

Inhaled beclomethasone dipropionate symposium

We have read with great interest in a recent *Respiratory Medicine* supplement (1998, volume 92, Supplement A) the series of papers presented at a symposium on inhaled beclomethasone dipropionate (BDP). These papers all describe a novel formulation (Qvar, 3M Healthcare) of BDP containing hydrofluoroalkane-134a (HFA-134a), which has been developed in response to the banning of chlorofluorocarbon propellants under the Montreal Protocol. The clinical efficacy data on Qvar, notably the study by Davies *et al.* (1), provide the basis for the use of lower BDP doses when given as the Qvar formulation to achieve a given anti-asthma response, while Qvar had less effect on the HPA axis than the CFC formulation (2).

These findings could be predicted qualitatively on the basis of a higher fine particle fraction and higher lung deposition for Qvar. However, the lung deposition data (3) show the remarkable result that only 4% of the delivered (ex-actuator) dose is deposited in the lungs for a CFC-formulation of BDP, while 51% of the dose is deposited in the lungs for the HFA formulation. It is debatable which of these two deposition figures is the more surprising. Mean lung deposition with correct inhaler technique has been shown to vary considerably according to formulation (4), but no other mean lung deposition data for inhaled asthma products delivered from pressurized metered dose inhalers without spacer devices, and inhaled correctly, are as low as 4% or as high as 51% of the delivered dose. It must be borne in mind that these deposition values are both expressed as percentages of the ex-actuator dose, and that they can only be compared directly if the ex-actuator doses for the two products are the same, which may well not be the case in this instance.

Attention to technical issues is essential if accurate lung deposition data are to be obtained. Scintigraphic studies are customarily performed using the radionuclide ^{99m}Tc, which is physically associated with the drug particles or droplets. As an essential prerequisite to the scintigraphic study itself, *in vitro* validation measurements are carried out using a particle sizing device such as an Andersen sampler, to show that the drug and radiolabel are associated together in particles or droplets of different sizes. Once this has been demonstrated, it may be assumed that the quantification of the radiolabel distribution will effectively quantify deposition of the drug itself. There are no validation data presented in Leach's paper (3), but validation data have been provided previously for the HFA formulation (5), showing a good agreement between the drug distribution before labelling, the drug distribution after labelling, and the distribution of the radiolabel. Cross-reference is made to an earlier abstract as the source of validation data for the CFC formulation (6), but this abstract only provides data comparing drug distributions before and after labelling, and does not compare radiolabel and drug distributions. To the best of our knowledge, no full published validation data comparing drug and radiolabel distributions have been presented for the CFC product, other than those appearing in the earlier paper by Leach (5). These data (Figure 4 of Leach's 1996 paper) showed a marked mismatch between drug and radiolabel distributions for the CFC formulation. One way of quantifying similarities or differences between drug and radiolabel distributions is to extrapolate from the approach used to show the similarities or differences between two dissolution curves for orally administered products (7), where the United States Food and Drug Administration recommend that an 'F-2' statistic is calculated. Two distributions are deemed to be similar if F-2 is >50. We have applied this approach to drug and radiolabel distribution data generated in validation experiments, and have found that distributions which match show an F-2 value between 60 and 100 (unpublished observations). An analysis of the data in figure 4 from the paper by Leach (5) provides an F-2 value of about 40. Curiously, Leach (3) comments in his discussion that he has 'great confidence' in his results, while going on to say that because of labelling problems the CFC data are 'less precise' than the HFA data.

In his studies, Leach (3) has made no correction to the data obtained for either CFC or HFA product to allow for the effects of overlying tissue on the attenuation of the gamma ray count reaching the gamma camera. We have shown that failure to allow for the effects of tissue attenuation causes lung deposition to be significantly underestimated (8). It has been claimed that no validated method exists for making a tissue attenuation correction, but this is incorrect. There are at least three methods which can be used to make this correction, involving transmission scanning (9), injection of a known amount of ^{99m}Tc-macro-aggregated albumin as a calibration dose (10), and the use of correction factors based upon individual body thickness measurements (11). We compared these methods (8), and showed that providing an appropriate tissue attenuation correction is made, it is possible to quantify the deposition of a known amount of radionuclide in the lungs to within about 5% of the true figure. Lung deposition data agreeing with those obtained by a second independent method may be obtained (12), assuming a tissue attenuation correction is applied to the scintigraphic data. Since different sites (lungs, stomach and oropharynx) attenuate gamma rays to

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different extents, it becomes especially important to make corrections for tissue attenuation when the relative amounts of lung and oropharyngeal deposition are expected to be different for the two products, and it will not be satisfactory to make no correction on the basis that subjects act as their own controls. In addition, failure to correct for tissue attenuation will produce data that cannot be compared directly with those obtained elsewhere for other products.

Based upon the above considerations, it is probable that the 13-fold difference in lung deposition values between CFC and HFA products reported by Leach (3) is caused in part by inaccurate quantification of the data, especially for the CFC product. Earlier this year, a workshop was held in London under the auspices of the British Association for Lung Research, which set out guidelines to ensure the correct conduct of scintigraphic studies in terms of their design and technical aspects, and to allow data obtained in different scintigraphic centres to be compared more readily. Amongst these guidelines was the need to generate and display adequate radiolabelling validation data for all products tested, and the need to make corrections for the effects of tissue attenuation of gamma rays. The workshop report has been published in *Respiratory Medicine* (13). There are plans to revisit these issues at another workshop to be held as part of the international Society for Aerosols in Medicine bi-annual congress in Vienna in June 1999.

The clinical response to inhaled corticosteroids is very difficult to measure, since these drugs act over relatively long time periods, and have flat dose response curves. The quantification of lung deposition data for inhaled asthma drugs can serve as a valuable surrogate for clinical response, but only providing that the technical issues associated with quantification of the deposition data have been addressed appropriately.

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Reply to Drs Newman and Pitcairn

We have read the 'Letter to the Editor' tendered by Drs Newman and Pitcairn regarding our paper in *Respiratory Medicine* (1), and we offer the following response. Dr Newman refers to the fact that detailed technical support of some of the data presented was not provided in the manuscript. The articles published in the supplement represent verbal overviews of many clinical studies presented in a symposium at the 1997 *European Respiratory Society Meeting* in Berlin. As such, the detailed experimental methods of all of the studies cited would have required several volumes of *Respiratory Medicine* to present. Obviously this is well beyond the scope or intention of the Supplement. Dr Newman has therefore chosen to go back to abstracts that represent a small portion of the work presented and criticize the techniques. Complete details of two of the studies cited in the symposium are presented in a recent article published in the *European Respiratory Journal* (2) and many of the issues raised are addressed there. However, the authors would like to address the specific questions raised here.

The authors agree that the essential element of any radiolabelled deposition study is the validation of the association of the radiolabel with the drug. Toward that end, the authors developed the Andersen Impactor